Response

Claims 1-44 are pending. Claims 1-44 are rejected. Claim 16 is amended to remove the repeated word "and" in the first line of the claim. No new matter has been added.

Response to Claim Rejections Based on 35 USC § 103(a)

Claims 1-44 are rejected as being unpatenable over the combined teachings of JP 3-56415 and US 6,602,911 (Kranzler *et al.*). The Examiner contends that the difference between JP 3-56415 and the instant application is that JP 3-56415 "contains structurally similar compounds [but] ... does not mention combination with other drugs for administration." The Examiner further contends that US 6,602,911 teaches the combination with other drugs. The Applicants respectfully disagree.

Firstly, the Applicants would like to state on the record that claims 1-15 and 18-34 are not related to combination therapy and thus the Applicants believe they should not be rejected based on the Examiner's arguments. Only claims 16, 17 and 35-44 deal with the compounds of the instant invention combined with another drug.

Secondly, the Applicants wish to make clear that claims 1 and 2 of the instant invention (along with dependent or related claims 3-44) are to *single* enantiomers, i.e., non-super-imposable mirror-image compounds. Importantly, neither JP 3-56415 nor US 6,602,911 disclose single enantiomers, also known as enantiopure compounds. For example, in JP 3-56415, the compound shown on page 109 is clearly a racemate, i.e., a 1:1 mixture of two enantiomers. In addition, the registry compound cited by the Examiner (No. 136091-14-0; belonging to JP 3-56415), while showing stereochemistry in the figure, is clearly labeled as depicting "relative stereochemistry" (directly above the pictorial depiction of the compound), as opposed to "absolute stereochemistry". Further, in US 6,602,911, the milnacipran disclosed is clearly labeled (column 6, lines 1-2) as "cis-(±)-2-(aminomethyl)-N,N-diethyl-1-phenyl-yclopropanecarboxamide" indicating that it is a racemic mixture, i.e., a 1:1 mixture of both the (+) and (-) forms.

Lastly, the Applicants argue that disclosure of racemic milnacipran, even if in combination with other drugs, does not render obvious any of the instant claims to enantiopure milnacipran or analogues thereof or methods of use in combination with other therapeutics. For

example, racemic para-hydroxy-milnacipran has distinct characteristics from enantiopure para-hydroxy-milnacipran; this fact is taught in the instant application (page 4, lines 17-23):

> Biological assay studies revealed that (+)-*para*-hydroxy-milnacipran is an approximately two-fold more potent inhibitor of norepinephrine uptake compared to inhibition of serotonin uptake. In contrast, (–)-*para*-hydroxy-milnacipran is an approximately two-fold more potent inhibitor of serotonin uptake compared to inhibition of norepinephrine uptake. The inhibition properties of each enantiomer of *para*-hydroxy-milnacipran stand in contrast to that of the racemic mixture which inhibits serotonin uptake and norepinephrine uptake with approximately equal potency.

Accordingly, the Applicants respectfully request the withdrawal of the rejections of claims 1-44 based on 35 USC § 103(a).

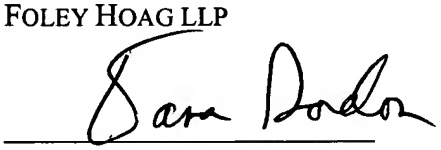
Fees

The Applicants believe no fee is required in connection with the filing of this paper. Nevertheless, the Director is hereby authorized to charge any required fee to our Deposit Account, **06-1448**.

Conclusion

In view of the above amendments and remarks, it is believed that the pending claims are in condition for allowance. The Applicants respectfully request reconsideration and withdrawal of the pending rejections. The Applicants thank the Examiner for careful consideration of the present case. If a telephone conversation with Applicants' Attorney would expedite prosecution of the above-identified application, the Examiner is urged to contact the undersigned.

Respectfully submitted,
FOLEY HOAG LLP



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